Crofelemer in the Treatment of Secretory Diarrhea

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Crofelemer, previously known as SP-303, is a novel proanthocyanidin purified from the bark latex of the Amazonian Croton tree *Croton lechleri.* Worldwide patent applications for enteric coated capsules have been filed for its use as an inhibitor of secretory diarrhea. Clinical studies (conducted under ICH GCP) involving 1,400 patients in double-blinded, placebo-controlled studies have establish that the drug is well tolerated and effective in mitigating travellers' diarrhea, and the chronic diarrhea of HIV/AIDS.

Crofelemer is an inhibitor of the cystic fibrosis transmembrane regulator chloride channel, as evidenced by its activity on cell cultures, single cell patch clamps, single CFTR channels, and elaboration of mouse intestinal fluid secretion. No effect was found on adenylate cyclase activity, or cAMP, indicating that crofelemer acts directly on the known mechanism of cholera and enterotoxigenic *Escherichia coli* fluid secretion in humans, and presumably other agents of secretory diarrhea that use the CFTR mechanism of diarrheagenesis. Extensive preclinical toxicology studies have been undertaken, including 32-day rat studies, 30-day dog, 9 month dog, Ames test, rat micronucleus, chromosomal aberration, rat fertility, embryo/fetal studies in rats and rabbits, and both pre- and postnatal development in rats.

A Phase II double-blind, randomized, placebo-controlled trial conducted at Jamaica (122 patients), Mexico (49), and US Border Towns (13) evaluated placebo, 125 mg, 250 mg, and 500 mg of crofelemer in a four-armed study over 2 days of treatment and one day of observation. The efficacy endpoints used were TLUS72 (time after last unformed stool), proportion of patients who were no better or worse after 24 hours, and symptomatic improvement, including changes in urgency and abdominal pain. Significant improvements were seen with all doses compared to placebo control in TLUS72, and significant reduction in treatment failures were seen over placebo controls. Moderate/severe abdominal pain and urgency improvement was also seen in the 250 mg group. After the first 24 hours of treatment, 91.3% of patients receiving 250 mg vs 65.9% patients receiving placebo were partial or complete responders ($p=0.003$).

A Phase II double-blind, randomized, placebo-controlled trial in HIV-associated diarrhea administered 500 mg crofelemer or placebo to 51 patients with HIV/AIDS (25 placebo, 26 crofelemer). Significant reductions were seen in stool weight ($p=0.008$), stool frequency ($p=0.04$), and stool chloride concentration ($p=0.04$). In a Phase III study of crofelemer in HIV-associated diarrhea in 400 patients with HIV/AIDS, four arms comprising placebo, 250 mg tablets, 500 mg tablets, and 500 mg beads were compared. Initial analysis showed borderline significance ($p=0.03$ vs. required of $p=0.015$), however reanalysis of patients with significant diarrhea at baseline (defined as watery stool and urgency at baseline) showed significant differences for change in stool weight ($p=0.01$), stool frequency ($p=0.02$), and frequency of loose/watery stools ($p=0.003$). The supply of raw material for crofelemer production has been assured through a huge natural stock of croton, sustainable harvesting research and the addition of 300,000 of these fast-growing trees through reforestation programs. Over $1M has been invested in long-term supply efforts.

Present plans include commercial manufacturing, and a Phase II proof-of-concept trial for effectiveness against cholera, and a confirmatory Phase III trial in HIV-associated diarrhea in 2006-2007.

In conclusion, crofelemer offers a natural product inhibitor of secretory diarrhea through inhibition of the CFTR chloride transporter. Crofelemer is not an antimicrobial, and therefore does not drive the emergence of resistance, it does not inhibit motility, and therefore does not cause constipation or rebound diarrhea, and it is not systemically absorbed, reducing the potential for adverse drug interactions and toxicity. Future research should address:

- Demonstration of efficacy against cholera
- Evaluation of safety and effectiveness in children and infants
- Impact on normal intestinal flora
- Comparison between patients and controls to evaluation of seroconversion of individuals convalescent from travelers' diarrhea, so determine if crofelemer inhibits colonization, or if colonization proceeds and provides convalescent immunity.